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AN INVESTIGATION
OF THE
RELATIVE RATE OF REDUCTION OF
NITROBENZOIC ACIDS.

A Dissertation presented to the Board
of University Studies of the Johns Hopkins
University for the Degree of Doctor of Phi-
losophy

by

William N. Berkeley

--O--

Baltimore, Maryland,
June, 1899.

Contents.

	Pages.
Acknowledgement.	3
Historical Sketch.	4
Material studied.	7
Preparation of Material.	7
Method of Proceedure,	9
Percentages of Reduction with weaker Solution.	16
Ratios between Reduction of Isomers.	19
Percentages of Reduction with stronger Solution	20
Differences of Reduction in successive periods.	21
Ratios between Reduction of Isomers.	23
Remarks on Results obtained.	23
Review of similar Investigations.	30
General Conclusions.	70
Biographical.	73

Acknowledgement.

This investigation was undertaken at the suggestion and prosecuted under the immediate supervision of Doctor Ira Remsen, to whose direction and counsel I gladly make this acknowledgement of my obligation.

To Doctor Morse my thanks are also due, for his guidance throughout the course in Analytical Chemistry, pursued under his supervision, and also for his advice on matters more directly connected with this investigation.

I am also indebted to Doctors Mathews^r and Ames^r for the benefits derived from their instruction and advice.

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HISTORICAL.

(1)

In an article by H. Limpricht appearing in 1878, and entitled "Reduction der Nitroverbindungen mit Zinnchlorür und quantitative Bestimmung der Nitro Gruppe", he gives the results of some investigations conducted by his two pupils, Heinzelmann and Altmann, on the use of stannous chloride and iodine solutions as a means for the quantitative determination of the nitro group in organic compounds.

Such determinations were made of the nitro group in meta-nitro-sulphobenzoate of sodium and its ortho-isomer. Also in para-nitro-sulphobenzoate of ammonium, ortho and meta-nitro-benzoic acid, meta-nitrobenzoate of barium, nitro-brombenzoic acid, dinitro-sulphobenzoate of barium, nitro-sulphobenzoate of potassium, meta-nitro-sulphobenzamide ortho-nitrophenol, meta-dinitrobenzene, nitro-bromsulphobenzoate of potassium and of ammonium, para-nitrotoluene, meta nitroanilin₉, etc.

The results of these investigations were such as to lead Limpricht to suggest the general applicability of the method, not only for purely scientific purposes but also to those of a technical nature. Later, in an article by S. H.

(1) Ber. XI., 35.

(1)

Young and R. C. Swain, "On the Volumetric determination of the Nitro group in organic compounds", the results of determinations of the nitro group in dinitrobenzene by means of stannous chloride and iodine solution are given, and the authors express the opinion that the method will prove generally applicable to other similar problems.

The article of Limpricht suggested the method as one that could possibly be used in the determination of the relative rate of reduction of the isomeric nitro bodies, and an investigation was begun following this suggestion ⁱⁿ by Remsen and Burton at the Johns Hopkins University, ~~On~~ the relative rate of reduction of ortho, meta, and para-nitrobenzoic acids. No conclusive results were obtained and the work described in this paper is a continuation of that investigation, and like that, was undertaken at the suggestion and prosecuted under the supervision of Dr. Remsen, ^{in the hope} ~~hoping~~ that the method mentioned might prove useful in the solution of this and similar problems.

MATERIAL USED AND ITS PREPARATION.

The substances studied, as already stated, were the three isomeric nitrobenzoic acids, it being originally intended to extend the investigation to a number of other ni-

(1) ~~Am.~~ Amer. Chem. Soc. ~~Trans.~~ ^{Proc.} Oct. 1897.

tro bodies.

The ortho and meta acids were prepared according to (1) the method described by Levy with certain modifications suggested by Mr. E. E. Reid, Fellow in Chemistry at this University. The para acid, being obtained in a very small percentage by this method, was prepared by another one, (also recommended by Mr. Reid) which consisted in oxidizing para-nitro-toluene by means of sodium bichromate and sulphuric acid. By means of repeated crystallizations from water, to which a little potassium permanganate was added, the three acids were obtained in a state of purity as was shown by their constant and sharp melting-points.

METHOD OF PROCEEDURE.

Owing to the extreme sensitiveness of the stannous chloride, to any change in the conditions under which the determinations were made, no little difficulty was experienced in maintaining from day to day such constancy in the conditions as would furnish results reasonably concordant.

The stannous chloride used in the reduction was made every day from the salt, crystallized just before each se-

(1) Anleitung zur Darstellung organisch-chemischer Präparate, pp. 158, et seq. (4th Edit.)

ries of determinations by quickly cooling a hot and concentrated solution by means of a freezing-mixture.

The iodine solution was kept in a metallic case to protect it as far as possible from all light, and was titrated against sodium hyposulphite, which, in turn, was standardized every day or two with iodine very carefully dried, sublimed, and preserved in a desiccator.

In the first determinations, the iodine equivalent of five cubic centimetres of the freshly prepared and unheated stannous chloride solution was determined and from this number was subtracted the number of cubic centimetres of the iodine solution required by each sample of the acid after reduction, but it was soon seen that this method of procedure made no allowance for the oxidation of the stannous chloride during the subsequent heating so this was changed, as will be described later. A great many sources of error were detected in the original method, and these were eliminated as far as possible.

The method after the elimination of a number of sources of error was as follows:-

Into three (3) flasks of about one hundred and twenty-five (125) cubic centimetres capacity, and each containing fifty (50) cubic centimeters of water, were weighed

from one to two-tenths (0.10 - 0.20) of a gramme of the isomeric acids. After the solution of the three (3) samples, these three (3) flasks, together with a fourth containing fifty (50) cubic centimeters of water alone, were transferred to a specially devised water-bath consisting of a smaller fitted into a larger one, the latter being heated by a Bunsen flame, which, when necessary, was controlled by a (1) thermostat.

After the flasks had been brought to the temperature at which it was proposed to determine the reduction, and the maintenance of this temperature was assured, fifty (50) cubic centimeters of an acid solution of stannous chloride, previously heated in a closed vessel to the same temperature, were added to each flask which was then securely closed with a stopper.

At intervals of one-half, one, one and a-half and two hours from the time at which the stannous chloride had been added to the respective flasks, samples containing approximately twenty-five (25) cubic centimeters were taken from each; quickly cooled by immersion in ice-water; ten cubic centimeters measured into a beaker, and, after adding fifty (50) cubic centimeters of water, two (2) cubic centi-

(1) This thermostat was kindly made for me by Mr. C. E. Waters, lecture assistant.

(1)

meters of soda solution, and ten (10) drops of a dilute starch solution, the excess of stannous chloride in each sample was determined by means of a N 1/100 iodine solution.

From the number of cubic centimeters of the iodine solution, representing the iodine equivalent of five (5) cubic centimeters of the stannous chloride solution, heated for the same time and under the same conditions of temperature and dilution as the sample of acid, was subtracted the number of cubic centimeters of the iodine solution required by each sample after reduction.

The difference multiplied by the weight of the nitrobenzoic acid corresponding to each cubic centimetre of the iodine solution gives the weight of the acid reduced from which the percentage of reduction is readily calculated.

In the following tables are given the figures representing the percentage of reduction after the samples had been heated at the temperature and for the time noted.

They represent the average of several hundred deter-

(1) Na_2CO_3 180 gms.
 Rochelle Salt 240 gms.
 H_2O qs. ad. 1 Li

minations, those which were obviously inaccurate from any known irregularities in the determination being excluded.

Using a stannous chloride solution containing eight (1)
(8) grammes of the tin salt to the litre -

RESULTS. HEATING THIRTY (30) MINUTES

Temperature	68° 70°	78° - 80°
Ortho acid	3.4%	12.1%
Meta "	1.0%	5.5%
Para "	10.0%	24.0%

HEATING SIXTY (60) MINUTES AT ABOVE TEMPERATURE

Ortho acid	12.1%	23.7%
Meta "	8.0%	17.4%
Para "	27.8%	39.0%

HEATING NINETY (90) MINUTES - SAME TEMPERATURE

Ortho acid	19.9%	33.6%
Meta "	13.0%	25.9%
Para "	34.1%	46.1%

(1) Two solutions were used at different times.

(a) SnCl_2 8 gms.
HCl 100c.c.
 H_2O q.s.ad 1 Li.

(b) SnCl_2 16 gms.
H Cl 100c.c.
 H_2O qs. ad 1 Li.

HEATING ONE HUNDRED AND TWENTY MINUTES

Temperature	68° - 70°	78° - 80°
Ortho acid	21.7%	38.5%
Meta "	16.9%	31.4%
Para "		52.2%

Numbering the intervals of thirty (30) minutes 1.2 and 3 and subtracting the percentages of reduction in successive equal intervals, we get the following differences

Temperature	68° - 78°		
	I.	II.	III.
Ortho	8.7%	7.8%	1.8%
Meta	8.0%	5.0%	3.9%
Para	17.5%	6.3%	-

For a temperature of 78° - 80° we get:

	I.	II.	III.
Ortho	11.6%	9.9%	4.9%
Meta	11.9%	8.5%	5.9%
Para	15.0%	7.1%	6.1%

In a similar manner, determining the ratio of the percentages of the isomeric acids reduced in the equal in-

tervals of time, and at the same temperature, we get (omitting the figures for the first thirty (30) minutes) the ratio ortho:meta: para

Temperature	68°- 70°	78°- 80°
after sixty minutes	1.5: 1:3.5	1.4: 1: 2.2
" ninety "	1.5: 1:2.6	1.3: 1: 1.8
" one hundred		
and twenty minutes	1.3:1:-	1.2: 1: 1.7

Using a solution of stannous chloride twice as strong as the above, i.e., containing sixteen (16) grammes of the tin salt to the litre, we get the following

RESULTS - HEATING THIRTY (30) MINUTES

Temperature	60°- 61°- 70°-71°- 80°- 81° - 87°- 88°			
Ortho acid	9.25%	20.4%	31.6%	42.6%
Meta "	2.8%	12.4%	-	38.3%
Para "	-	27.7%	55.6%	68.8%

HEATING ONE HOUR - TEMPERATURE AS ABOVE

Ortho acid	12.5%	34.6%	43.4%	56.1%
Meta "	3.9%	26.7%	37.6%	50.2%
Para "	-	40.7%	59.4%	79.0%

HEATING ONE AND ONE-HALF HOURS

Temperature	60° - 61°	-	70° - 71°	-	80° - 81°	-	87° - 88°
Ortho acid	21.2%		42.0%		50.0%		61.0%
Meta "	11.6%		32.5%		44.9%		56.4%
Para "	-		68.0%		-		80.4%

HEATING TWO (2) HOURS

Ortho acid	28.3%		-		54.8%		63.4%
Meta "	17.4%		-		50.2%		60.4%
Para "	-		-		69.8%		82.6%

As before numbering each successive interval of thirty (30) minutes 1,2,3, and subtracting the figures representing the percentages of reduction in these successive intervals we get the following

RESULTS - TEMPERATURE 60 - 61

	I.	II.	III.
Ortho acid	3.25%	8.7%	7.1%
Meta "	11.0%	7.9%	5.8%

RESULTS - TEMPERATURE 70 - 71

	I.	II.	III.
Ortho acid	14.2%	7.4%	-
Meta "	14.3%	5.8%	-
Para "	13.0%	27.3%	-

RESULTS - TEMPERATURE 80 - 81

	I.	II.	III.
Ortho acid	1.8%	6.6%	4.8%
Meta "	-	7.3%	5.3%
Para "	3.8%	-	-

RESULTS - TEMPERATURE 87 - 88

	I.	II.	III.
Ortho acid	13.5%	4.9%	2.4%
Meta "	11.9%	6.2%	4.0%
Para "	10.2%	1.4%	2.6%

Comparing as before the figures representing the percentage of reduction of each of the acids in each period of thirty minutes we have the ratio ortho ; meta; para

TEMPERATURE - 60°- 61° - 70°- 71° - 80°- 81° - 87°- 88°

Heating sixty minutes 3.2:1:- 1.3:1:1.5 1.1:1:1.6 1.1:1:1.6

" ninety " 1.8:1:- 1.3:1:1- 1:1:- 1+:1:1.4

" one hundred and

twenty - 1.6:1:- - 1+:1:1.4-1+:1:1.4

The great irregularities noted in comparing the figures expressing the reduction in the early stages of the reaction, are no doubt attributable to the fact that some considerable time was necessary to get the reaction well

underway, and, as the figures show the meta acid to be less susceptible to the action of the reducing action, and especially so at the lower temperature, this would naturally present the greatest irregularity, a fact shown by the figures expressing the percentages of reduction.

By far the greater number of determinations were made with the weaker solution of stannous chloride, and as it was found that the reaction at temperatures below sixty (60) degrees was very slow, (no reduction being detected even at the end of two (2) hours in the case of the meta, or at the end of one (1) hour in the case of the ortho acid) subsequent determination were made at temperatures varying from 70° - 38°

It will be seen from the description of the method of procedure, that the figures representing the percentages of reduction are necessarily based on the assumption that the stannous chloride, in each of the flasks containing the acids to be reduced, is oxidized to the same extent, in the course of the heating, as it is in the flask containing the stannous chloride alone; but while this assumption is necessarily made, it is not unreasonable to suppose that not only the presence of the organic acid in the stannous chloride solution, but also the extent to which this is suscepti-

ble to reduction may influence the extent to which the stannous chloride is oxidized.

We might, therefore, conclude that the amount of reduction of the organic acid is determined to some extent by the greater or less loss in the efficiency of the tin salt through its oxidation, this in turn being influenced, as just stated, by the greater or less ease with which the acid in question undergoes reduction.

Some weight seems to attach to this hypothesis, from some observations made in regard to the rather peculiar behavior of the meta acid especially at lower temperatures.

It was found, for example, that in certain determinations samples of this acid, taken and titrated as usual after heating with the stannous chloride required more iodine than a sample of the tin salt heated alone.

The recurrence of this phenomenon throughout a whole series of samples, taken at intervals of one-half hour for two hours, precludes the possibility of assigning it to analytical errors.

This could be explained, ^{however,} ~~though~~ by the hypothesis that the tendency of the meta acid to be reduced had lessened the susceptibility of the tin salt to be oxidized

which would, therefore, undergo oxidation to a less extent than the stannous chloride heated alone.

The fact already stated, that the meta acid at the lower temperature seems very sluggish appears to indicate that the two opposing forces, tending to oxidation on the one hand and to reduction on the other, tend to neutralize one another until sufficient time has elapsed to start the reaction between the tin salt and the acid.

This apparent inertness of the meta acid is of course in complete accord with the general conclusions adduced from the whole series of determinations as to the less susceptibility of this acid to the reducing action.

These conclusions are based on the results of a long series of determinations performed with great care.

The figures given in this paper are decidedly surprising, viewed in the light of results obtained in investigations conducted along somewhat similar lines, from which it appeared that the presence of certain groups in a variety of organic compounds, which were in the ortho position relative to certain residues seemed to exert over these latter a protective influence to a greater or less extent, when subjected to the influence of certain classes of re-

agents.

REVIEW OF SIMILAR INVESTIGATIONS.

That the introduction of certain elementary or compound molecules into organic bodies influenced their stability has been long known but only such investigations shall be discussed in this paper as are more immediately related to the problems described therein.

(1)

As early as 1867 Vollrath called attention to the marked stability of tri-chlor-xylene against the oxidizing action of chromic acid.

(2)

In this same year, also, Beilstein and Kreusler showed that when nitroxylene from coal-tar xylene was oxidized it formed nitrotoluic acid, and they add, in no case is the second methyl group of nitroxylene attacked by this oxidizing agent.

(3)

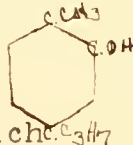
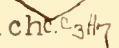
In 1871, Rudolph Fittig in an article entitled "Gesetz^amässigkeiten in der Aromatischen Gruppe" states that it seems at least very probable that all ortho compounds, when treated with chromic acid mixture, do not furnish the oxidation-products corresponding to the analogous meta and para bodies but are entirely decomposed and he

(1) Zeitschf für Chemie, VII, 179 (1870). (2) A.144, 168.

(3) A.144, 266.

adds that Beilstein had found that the oxygen, chlorine, iodine and nitro derivatives of toluene treated with chromic acid mixture do not form the corresponding benzoic acids but are burnt up.

(1)

Again, in 1878, E. v. Gerichten showed that when chlor-cymene made from carvacrol  is oxidized it passes to chlor-toluic acid in which  the position of the chlorine is ortho to the methyl and meta to the propyl group, the latter only being oxidized to the carboxyl group.

(2)

Schmitz, also, in 1878, in studying nitro-mesitylenic acid found that the two methyl groups which remained unoxidized were in the ortho position relative to the nitro group and in brom-mesitylenic acid the same relative positions was proved.

In the mean time there appeared in 1873 the first
(3)

of a ~~long~~ series of articles by Dr. Ira Remsen, then at Williams College, in which are given the results of a long series of investigations, conducted for the most part by Dr. Remsen and his students at the Johns Hopkins University, and in which the whole question of the protective influence of certain negative groups in an ortho position relative to

(1) Ber.XI., 364.

(3) Am. Jour. Sci., V. 354.

(2) A. 193,160.

certain oxidizable residues, was very elaborately investigated, the results being published in a series of articles under the general heading "On the Oxidation of Substitution Products of Aromatic Hydrocarbons".

The conclusions drawn from these investigations
(1)
are expressed thus:

"The results thus far reached all agree, and they make the conclusion extremely probable, that in all cases now on record, in which hydrocarbon residues are shown to be protected from oxidation by the presence of negative groups, the latter are in the ortho position with reference to the former, whereas, oxidizable residues when situated in the meta or para positions with reference to the negative groups are, under the same circumstances, transformed just as if the negative groups were not present."

Some of the facts upon which these conclusions were based are these:

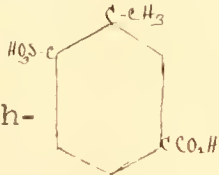
First, it was found that when a mixture of ortho and para-toluene sulphonic acids was subjected to the oxidizing action of chromic acid mixture, it yielded no orthosulphobenzoic acid, and when the potassium salts of ortho- and para-

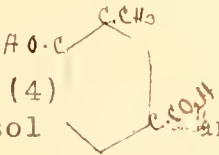

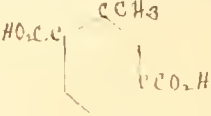
(1) Am. Chem. Jour., I., 36.

(2) Am. Chem. Jour. I., 32.

toluenesulphonic acids were treated separately in the same way, the action in the case of the para compound was prompt and vigorous, while in the case of the ortho isomer it was sluggish and weak.

Again, ~~an~~ oxidizing orthotoluenesulphamide mixture (1) with a little of the para isomer the ortho was not at first affected, while the second passed into the corresponding sulphaminebenzoic acid, and continued action only served to partly destroy the ortho body.

Later it was shown that by the oxidation of metaxylenesulphamide (2) an acid was formed whose formula was shown to be  in which the methyl group ortho to the sulph-~~amic~~ic acid residue is protected from oxidation.

The correctness of the above formula was shown, (3) first; by its conversion into oxy-toluic acid whose formula is  (4) as is proved by its conversion into ortho cresol  and further the sulphamine~~metatoluic~~ acid (5) was transformed into xylinic acid 

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- (1) Am. Chem. Jour. I., 32 et. seq.
 (2) Am. Chem. Jour. I. 37.
 (3) Ibid. I., 48.
 (4) Ibid. I., 114.
 (5) Ibid. I., 119.

and also to isophthallic acid.

(1)

In a later article by Remsen and Morse they show that when brom-ethyl-toluene is oxidized by chromic acid mixture, it passes first to brom-ethyl-para-toluic acid, and then to para toluic acid, and the authors think that the resistance offered by the methyl group to the oxidizing agent is due to the fact that it is in an ortho position relative to the bromine.

(2)

Afterwards it was shown by Remsen and Hall that para-xylenesulphamide is oxidized to sulphamine-para-toluic acid, and while the author did not prove directly the relative positions of the group in this compound, they concluded that the unoxidized methyl group was in an ortho position relative to the sulphamine group from its analogy to cymene-sulphanide which is oxidized first to sulphamine-para-toluic acid, and then to the acid described by E. v. Gerichten under the names of ^{ortho} a-oxy-toluic-acid in which, as he showed, the hydroxyl group is in the ortho position relative to the methyl.

On the other hand, Remsen and Hall showed that mesitylene-sulphamide is oxidized to a sulphinide, and rea-

(1) Am. Chem. Jour. I., 138.

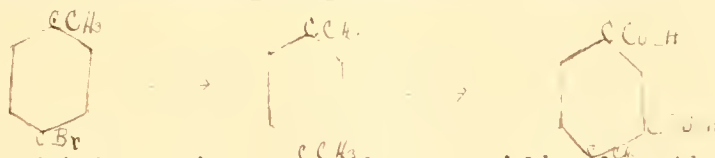
(2) Am. Chem. Jour. II., 50.

soning by analogy with other sulphinides, the acid from which the sulphinide came directly by elimination of water, must have had the carboxyl and sulphamide groups in the ortho position relative to one another. This, therefore, seems opposed to the theory of protection.

It was found later that cymene[^]sulphonic acid is converted by chromic acid mixture to an acid thought to be
(1)
identical with an acid described by Flesch which in turn passes into the oxy-toluic-acid of v. Gerichten.

(2)

Remsen and Kuhara describe the preparation of sulpho[^]para[^]toluic acid from para[^]brom[^]toluene, the transformations being represented graphically in this way



in which as is seen the unoxidized methyl group is ortho to the sulphonic acid residue.

Studying the influence of nitro groups ortho to
(3)

the oxidizable residue, they showed that nitrotoluic acid, when first converted into the corresponding amido-toluic acid, passes through the diazo compound into oxy toluic acid, which they showed to be identical with the oxy-toluic

(1) Ber. VI. 481.

(2) Am. Chem. Jour., 413. (3) Am. Chem. Jour. III. 424

acid prepared by Remsen and Hall, and with the ortho-homo-
 para-⁽¹⁾oxybenzoic acid of Tiemann and Schotten C_6H_3 ^{(OH) (1)} ^{(CH₃) (2)} ^{(CO₂H) (4)},
 from which it followed that the nitro-toluic acid is
 C_6H_5 ^{(NO₂) (1)} ^{(CH₃) (2)} ^(CO₂H), in which the oxidized and unoxidized methyl
 group is para and ortho respectively to the nitro group.

In commenting on this last investigation on the influence of nitro groups on an oxidizable residue the authors say:

"The facts thus far determined are not sufficient to warrant a satisfactory conclusion though they make an affirmative answer (i.e., one affirming the law of protection) probable, at least for such substances as contain two oxidizable residues together with the nitro group."

Finally, in an investigation conducted by Remsen ⁽²⁾ and Noyes with the object of discovering whether the protective influence of negative groups extended to groups more complex than methyl, they find that starting with diethylbenzenesulphamide they get, after a series of transformations, finally sulphamene-ethylbenzoic acid in which the sulphamine group was thought to be in the meta-position relative to the carboxyl.

⁽³⁾
 Remsen and Day also studied the effect of neg-

(1) B. XI., 767.




(2) Am. Chem. Jour. III., 20.

(3) Am. Chem. Jour. V. 148; IV. 197.

ative groups on propyl groups and found that by oxidizing
oxy-brom-cymene-sulphamide C_6H_3 $\begin{matrix} (\text{C}_3\text{H}_7 \\ (\text{SO}_2\text{NH}_2(\text{O}) \end{matrix}$ it passes to
 C_6H_3 $\begin{matrix} (\text{C}_3\text{H}_7 \\ (\text{SO}_2\text{NH}_2(\text{O}) \\ (\text{CO}_2\text{H}(\text{P}) \end{matrix}$ $\begin{matrix} (\text{CH}_3(\text{P}) \end{matrix}$ (1)

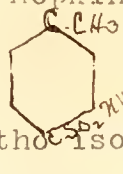
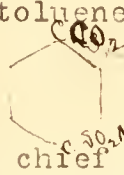
On the other hand, Remsen and Keiser found that
by the oxidation of para-dipropyl-benzoic sulphamide the
protection of the propyl group is not complete.

Among a great many others who worked on problems
similar to the one just described may be mentioned Richard
(2)

Meyer and A. Bauer who found that potassium permanganate
converted cymene sulphononic acid  into 
while with the use of nitric acid it formed  which Meyer cites as a confir-
mation of Remsen's protection theory.

Prof. K. Shimomura of Kyoto, Japan, continuing

some work commenced at the Johns Hopkins University found

that para-toluene-sulph-anilide  when oxidized
passes to  while the ortho-isomer gives
as the the chief product, these results

being in accord with results obtained by oxi-
dizing para- and ortho-toluene-sulphamide.

(1) Am. Chem. Jour. V., 160. (2) A. 220, 6.

(3) Private communication to Prof. Remsen.

(1)

W. A. Noyes also in an article entitled "On oxidation of benzene derivatives by potassium ferricyanide," says that all the work done on the oxidation of aromatic hydrocarbon derivatives leads to these conclusions: (1) chromic acid does not oxidize ortho groups or only to a slight extent. (2) Nitric acid can oxidize ortho groups but prefers meta or para groups. (3) Caustic potash, in the case of the only class of substances studied, oxidizes the groups ortho to the negative group. (4) Potassium permanganate in alkaline solution oxidizes ortho, meta and para groups preferring the para in some cases.

Noyes, as a result of his own experiments with potassium ferricyanide in alkaline solution, found that by treating ortho-nitrotoluene mixed with a little of the para isomer he got ortho and para-nitrobenzoic acid.

He finds that para-bromtoluene is oxidized with great difficulty and the ortho body with still more, if at all. He also notes that more than two and a half times as much para-nitrotoluene is oxidized than of toluene itself.

Another very important investigation, similar to those described above, is that of Victor Meyer and his co-workers the results of which were published in a series of -----

(1) Am. Chem. Jour. V., 97. (VII., 145; VIII., 167, 176; X., 472)

articles appearing in the Berichte of the German Chemical Society under the title of "Das Gesetz der Esterbildung der Aromatischen ⁽¹⁾sauren".

The results obtained tend to support the hypothesis of the protective influence of the ortho position.

Meyer was lead to undertake this investigation by his discovery of the fact that mesitylene carbonic acid when heated with methyl alcohol and hydrochloric acid gave no ester.

From his study of a large number of acids, he was lead to the conclusion that, whenever the carboxyl group of the acid is in the ortho position relative to two other groups, e.g., NO_2 , CH_3 , , OH CO_2H etc., they lose entirely or in part, their capacity for forming esters in the usual manner, i.e., by treating it with an alcohol and a mineral acid.

It will be noted that this complete protection of the carboxyl group occurs only when it is ortho to two other groups.

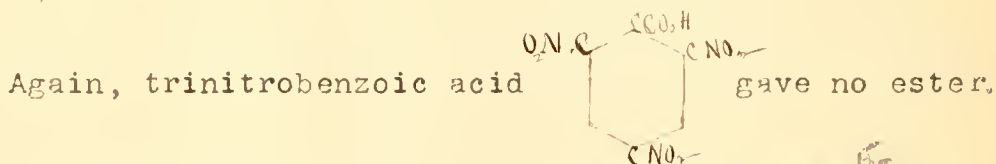
The problem involved in Meyer's work, as in that of the other investigators mentioned, differs very essentially in the nature of the reaction studied in these cases from that one studied and described in this paper.

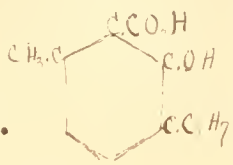
(1) B. 27,510,1580,3146-28,182,1254,2773,3197-29,839.

It also differs in this respect that, while in the former cases it was generally a negative group that seemed to exert the protective influence, in the latter, it is the negative group that is attacked by the reagent.

Some of the facts upon which Meyer based his conclusions were as follows:

First, as already stated, he found that mesitylene-carbonic acid in which the carboxyl is ortho to two methyl groups gave no ester when treated in the usual way while Duryl acid, its unsymmetrical isomer, yielded ninety per cent.



Studying the effect of the hydroxyl group on ester forming capacity of an acid, he found that salicylic acid, an ortho compound, gave ninety per cent of an ester only by heating (about 70°) while the para isomer yielded an ester with ease and the meta more slowly. On the other hand, thymotinic acid  is with difficulty made to yield an ester.

They conclude that in the case of the hydroxyl group, the protective theory can be applied only in a limited way.

Some of the trihydroxy acids form esters while phloroglucinic acid liberates carbon dioxide and forms an ether of phloroglucin.

Meyer tried to discover the cause of the non-esterification of the acids of the general formula $\text{RC} \begin{array}{l} \text{C.CO}_2\text{H} \\ \text{C.R} \end{array}$ ($\text{R} = \text{CH}_3, \text{NO}_2, \text{Br}, \text{OH}, \text{CO}_2\text{H}$ etc.) which he thought due to one of two causes; either to the presence of some or all of the substituents, or to the unreplaced hydrogen.

To decide these points they studied the acids formed by further substitution of the trisubstituted acids.

It was found that tetra-bromobenzoic acid $\text{BrC} \begin{array}{l} \text{C.CO}_2\text{H} \\ \text{C.Br} \end{array}$ gave no ester nor did the acid $\text{BrC} \begin{array}{l} \text{C.CO}_2\text{H} \\ \text{C.Br} \end{array}$ nor $\text{BrC} \begin{array}{l} \text{C.CO}_2\text{H} \\ \text{C.Br} \end{array}$. The dibrom-benzoic acid $\text{BrC} \begin{array}{l} \text{C.CO}_2\text{H} \\ \text{C.Br} \end{array}$ gave ninety per cent of an ester while its isomer $\text{BrC} \begin{array}{l} \text{C.CO}_2\text{H} \\ \text{C.Br} \end{array}$ gave none.

The conclusions drawn from these investigations (1) are expressed in these words:

"According to this, all questions that we have proposed above are experimentally answered. The results are unmistakable. As soon as two hydrogen atoms adjacent to a carboxyl are replaced by radicals, e.g., CH_3 , Br , NO_2 , etc, there results an acid which is not capable of forming an

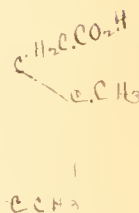
ester. The occurrence of the three substituents as well as of the two hydrogen atoms in trisubstituted benzoic acids is without influence on the phenomena".

Meyer proposes a rather unique hypothesis to explain why those acids which do not form esters in the usual way, that is, with alcohol and a mineral acid, do so when the silver salt of the acid is treated with an alkyl halide.

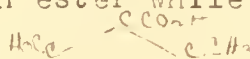
He thinks that when the silver atom enters the carboxyl group it, by virtue of its superior size, forces the adjacent groups aside to such a distance that they can not exert their protective influence.

As evidence confirming this view, he offers the following facts:-

He found that mesitylene¹acetic acid i.e.,

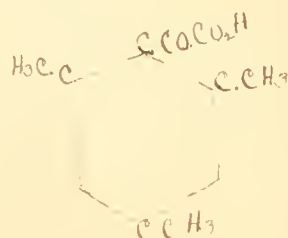


where the carboxyl group is removed from the immediate neighborhood of the methyl groups, forms ninety-six (96) per cent of an ester while, as already stated, mesitylene²carbonic acid



forms none.

Mesitylene³glyoxylic acid



also forms ninety-six percent (96%) of an ester.

It was also found that the carboxyl group itself exerts this protective influence where two are in an ortho position relative to a third as in mellitic acid

$\begin{array}{c} \text{HO.CC} \text{---} \text{C.CO}_2\text{H} \\ \text{CCO}_2\text{H} \end{array}$

(1)

which gives no ester. (Baeyer, on the other hand, found that hexahydro mellitic acid is capable of esterification)

$\begin{array}{c} \text{C.CO}_2\text{H} \\ \text{C.CO}_2\text{H} \\ \text{HO.CC} \end{array}$

Pre-mellitic acid also gives ninety-six per-
centage of an ester. Pre-mellitic acid

$\begin{array}{c} \text{C.CO}_2\text{H} \\ \text{C.CO}_2\text{H} \\ \text{C.CO}_2\text{H} \\ \text{C.CO}_2\text{H} \end{array}$

forms only a di-ester.

Investigating the two isomeric nitrophthallic acids

$\begin{array}{c} \text{NO}_2 \\ \text{C.CO}_2\text{H} \\ \text{C.CO}_2\text{H} \end{array}$

and

$\begin{array}{c} \text{C.NO}_2 \\ \text{C.CO}_2\text{H} \\ \text{C.CO}_2\text{H} \end{array}$

he found that the former gave a mono ester while the latter gave none.

(2)

Beilstein and Kurbatov had shown he says that the acid

$\begin{array}{c} \text{C.CO}_2\text{H} \\ \text{C.CO}_2\text{H} \end{array}$

forms a monoester, while, on the other hand, they confirmed Graeber's statement that tetrachlorophthallic acid gives an acid ester, while, according to the theory, it should not form any. That this was not due to the presence of the chlorine was shown by the fact that the chlorbenzoic acid

$\begin{array}{c} \text{C.CO}_2\text{H} \\ \text{C.CO}_2\text{H} \end{array}$

gave no ester while the isomer

$\begin{array}{c} \text{C.CO}_2\text{H} \\ \text{C.CO}_2\text{H} \end{array}$

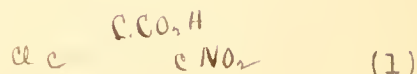
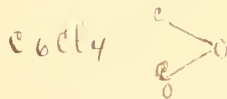
did.

Meyer suggested that the first phthallic acid might

(1) A. Sup'l. no. 7, 15). J. Van Loon (B. 23, 1270) says only isohydro mellitic acid forms an ester; he ascribes the difference in the behavior to a "cis" & "trans" form.

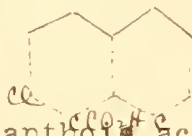
(2) A. 202, 207.

occur in two forms yielding two esters of the general formula C_6Cl_4 $\begin{matrix} -COOR \\ COOR \end{matrix}$ and C_6Cl_4 $\begin{matrix} OR \\ OR \end{matrix}$



Meyer also studied the acid

to see if an acid in which the carboxyl group is ortho to two unlike negative groups is capable of esterification. He found that in this case no ester is formed. He also found that an acid of the general formula C_6Cl_4 $\begin{matrix} CO_2H \\ CO_2H \end{matrix}$ ester. Meyer studied the two chlor naphthoic acids C_6Cl_4 $\begin{matrix} CO_2H \\ CO_2H \end{matrix}$ (4)



gave no ester

and found that the first gave no ester while the second one gave ninety per cent (90%) of an ester

(2)

Studying the rate of esterification of isomeric bodies he found the reaction was slowest in the case of the ortho compounds and the same thing was proved in regard to the rate of saponification.

(3)

In a later article though published with the above Meyer said that Behla had shown that the acid



gave no ester as was to be expected while

(1) B. 28, 182.

(2) B. 28, 188.

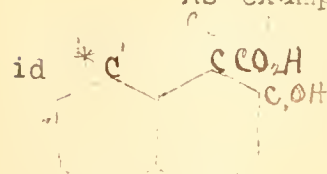
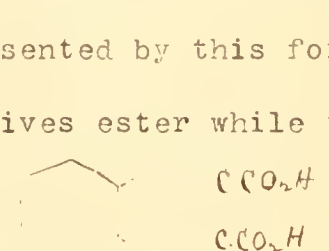

(3) B. 28

(4) * Carbon al situated thus seem to act as substituents.

(5) B. 20, 703.

Meyer himself proved that the chlorine-free acid also gave none.

Meyer, in a subsequent article, modifies his former views as to the influence of hydroxyl groups on esterification, and says that, if two positions ortho to a carboxyl are possessed by substituents, and if one of these is an hydroxyl, no ester is formed in the cold.

As examples of these he cites phenyl salicylic acid  and the acid represented by this formula  neither of which gives ester while the isomer of the latter one does, i.e., 

Meyer also gives as further proofs of his stereochemical hypothesis which he had offered to explain why acids in which the carboxyl group was immediately adjacent to two negative groups form no ester while they do if the carboxyl is separated from these by one or atoms or atom-groups the following facts:-

Representing the group $C_6H_2R_3CO_2H$ (in which R = Radical) by ms, i.e. mesitylene-like, he found that $MsC(CO_2H)_3$, $MsCO(CO_2H)_2$, $MsCO_2CH_2CO_2H$ and $MsCH_2CH_2CO_2H$ all gave esters.

Meyer also studied the difference in the effect

of various substituents on ester-forming, especially with reference to the relative weights of the substituent ~~as to~~ as to the relative intensity of their negative or other character. With reference to the first he says: "those radicals which prevented the formation of ester even under the influence of heat were found to have a far greater weight than those which prevented it only in the cold" As examples of the first class he cites the groups Cl, NO₂, Br, while in the second class he puts CH₃ and OH.

He also found that the esters of the acids and $\text{C}_6\text{H}_5\text{CO}_2\text{H}$ behave very differently towards saponifying agents, and states that "this surprising result shows distinctly that those esters that are formed with difficulty are saponified with still greater difficulty and vice versa".

Studying the rate of esterification he found that in the cases of ortho, meta-, and paratoluic acids, ortho-, meta-, and parabrom-benzoic acids and ortho-, and metanitro-benzoic acids, the ortho isomers ~~were~~ ^{were} acted on much less readily, while experiments on the rate of saponification of ortho- and metabrombenzoic acid esters gave similar results.

(*) He proved that carbon atoms so situated act as negative groups as regards their effect on ester-forming.

(1)

In an article by J. J. Sudborough on "Di-ortho substituted benzoic acids" he describes the results obtained in an investigation, first, on the relative stability of isomeric substituted benzoyl chlorides towards water and caustic soda and, secondly, on the behavior of isomeric aromatic nitrites and acid amides towards hydrolyzing agents.

Under the first head he gives the results of his study of ortho-, meta -, and parabrombenzoyl chloride of 2-4, 3-5, 2-6 dibrombenzoyl chloride of 2-4-6, and 3-4-5 tribrombenzoyl chloride and of 2-3-4-6 tetrabrombenzoyl chloride.

His conclusions based on the results of this investigation are stated thus: "The ortho chlorides in which the substitution does not occur in either of the ortho positions are readily decomposed by dilute alkalies, the decomposition being almost instantaneous at the boiling-point of the alkali solution.

(2) The acid chlorides which have a bromine atom in one ortho position are relatively more stable towards alkalies

* * * * *

(3) The acid chlorides in which both ortho positions are occupied by bromine atoms are only converted into the corresponding sodium salt of the acid by long continued boil-

(1) Chem. Soc. Jour. (Trans) 67,587,601.

ing with an alkali solution.

(4) If substitution has already taken place in the two ortho positions with respect to the COCl_2 group, the introduction of bromine atoms into the benzene nucleus seems to render the acid chloride still more stable."

In the second part of his article, Sudborough gives the results of a study of the behavior of 2-6 and 2-4 dibrombenzamide towards 80% sulphuric acid and says: the 2-4 amide differs from the 2-6 isomer in the readiness with which it is converted into the corresponding acid, the latter being characterized by its great stability towards hydrolyzing agents.

Claus and his pupils working on the hydrolysis of various aromatic nitrites⁽¹⁾ give results which for the most part accord with those of Sudborough.

Their experiments show that while most nitrites are hydrolyzed to the corresponding acids by boiling for several hours with 60%-70% sulphuric acid, those in which substitution occurs in the two ortho positions yield the acid amide and not the acid under the same conditions. Two important exceptions though, apparently, are 2-6 dichlor-benzonitrite and 2-4-6 methyl-chloronitrobenzo-nitrite".

(1) Jnl. fir Chemie. (2) 37,197, A. 265,266,269,274.

Wegschider also did some work on esterfication chiefly on hemipinic and opianic acids and decides that the difference in the behavior of acids towards alcohol and a mineral acid and that of their salt (Ag) towards alkyl halides is due to the fact that in the first case there is an addition of the acid, and that this addition is more interfered with by the neighboring ortho groups than is the substitution of the alkyl for the metal.

(1)

This theory of the addition of the mineral acid
(1) (2)
 though, seems to have been advanced first by Henry, Friedel thought that in making an ester by an alcohol and hydrochloric acid, a chloride was first formed and that the necessary splitting off of the hydroxyl of the organic acid was prevented by the presence of the ortho groups.

One of the most important and fruitful investigations dealing with this subject of the protective influence of ortho groups is one that was conducted by Remsen and Reid at the Johns Hopkins University "On the hydrolysis of the acid amides and their derivatives" the results of which have just been published.

The results of this investigation which was conducted with the greatest skill and was characterized by an -----
 (1) B. 10, 2041 (2) Zeitsch für Chemie. 12,488 (1869)

attention to the most minute details rarely found in similar work fully justified all the labor involved and furnished a great deal of evidence in support of the "protective theory".

Among the substances studied were: benzamide and its amido, chlor, hydroxy, brom methoxy, and ethoxy derivatives and the isomeric toluic amides.

The results of hydrolysis both with acids and alkalies went to ~~show~~ the very much greater stability of the ortho isomer towards these reagents.

About the same time that the above investigation by Remsen and Reid was being prosecuted, Kellas published (1) an article in which he gives the results of an investigation on the rate of esterification of certain organic acids.

He endeavored to discover (1) some definite rule for the rate of esterification of the ortho, meta and para acids - (2) Influence of temperature. (3) Influence of the atom or atom group on the rate.

He studied: ortho, meta, and para-toluic acids, ortho, meta, and para, nitro-chlor, brom, and iodo-benzoic acids, ortho, meta, and para-oxy-benzoic acids.

(1) Zeitschf für Physikalische Chemie. XXIV., 221.

Studying first chlor-, brom-, iodo-, and nitro- benzoic acids, he found that the rapidity of the rate of esterification was always ~~lost~~ in case of the ortho isomer, while the relation between the meta and para compounds changed more or less with the substituents. The isomeric ~~toluic~~ acids gave similar results. This relation was also maintained fairly well with changes in temperature..

Comparing the relative rates of reduction of all chlor-, brom-, nitro-, and iodo- derivatives, he found that the nitro ^{group} had by far the greatest retarding influence, while in the case of the iodo-, brom-, and chlor- derivatives, the retardation diminished in the order named.

Experiments on rate of saponification gave similar results.

GENERAL CONCLUSIONS DRAWN.

It is thus seen that by far the greater number of the experiments cited tend to show that the presence of certain groups in an organic compound occupying an ortho position relative to certain other groups affect in a greater or lesser degree their susceptibility to the action of certain classes of reagents.

That this protective influence varies in degree and kind with the nature of the reagent employed seems to be proved by a number of the investigations noted as well as by that forming the subject of this paper. While the results of this last investigation were not as satisfactory as it was hoped would be obtained, the constancy of the indications leaves no doubt as to the correctness of the conclusions reached, i.e., that the three isomeric nitrobenzoic acids ~~are~~, under the influence of an acid solution of stannous chloride, ^{are} reduced at a rate increasing from the meta to the para acid. The fact that with ~~an~~ increasing time and temperature the ratio of the amount of the ortho acid reduced to that of the meta acid diminishes is no doubt attributable to the more rapid loss of the reducing efficiency of the stannous chloride in contact with the more readily reduced organic acid.

Biography.

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The author of this dissertation was born at Aldie, Loudon county, Virginia, September 24, 1867.

His earlier education was obtained by attendance at the public schools of Albemarle county, Virginia, and later at public (High) Schools of Staunton, Virginia and at a private school at the same place.

He attended the University of Virginia, 1887-1888, 1891-2, and also for three summer sessions. He graduated there in the schools of Chemistry, Geology and Mineralogy, and for the year subsequent to his graduation was employed as Analytical Chemist at an Iron furnace in Pulaski City, Virginia.

In 1893 he was elected Professor of Chemistry at St. John's College, Annapolis, Maryland and held that chair till 1896, when the degree of B.S. (Hon) was conferred on him.

In 1896 he entered the Johns Hopkins University as a graduate student, and has for the past three sessions pursued courses in Chemistry, Geology and Physics, holding an ordinary Virginia Scholarship throughout this period.



